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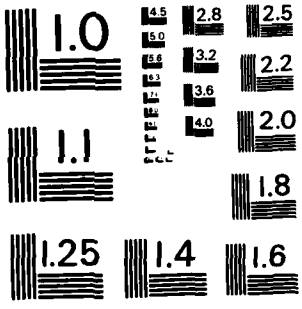

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This paper summarizes the findings from two recent studies involving the physiological effects of atropine (0-4 mg, i.m.) on soldiers performing physical exercise in hot-dry environments. Study I determined the threshold of physiological effects and the gradation of these effects with increasing dosage of atropine. Study II examined the effects of exercise-heat acclimation on the reduced physical exercise performance that occurs following atropine administration. The following new observations were made: (1) a 0.5 mg dose of atropine

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Effect of Atropine on the Exercise-Heat Performance of Man

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ABSTRACT

This paper summarizes the findings from two recent studies involving the physiological effects of atropine (0-4 mg, i.m.) on soldiers performing physical exercise in hot-dry environments. Study I determined the threshold of physiological effects and the gradation of these effects with increasing dosage of atropine. Study II examined the effects of exercise-heat acclimation on the reduced physical exercise performance that occurs following atropine administration. The following new observations were made: (1) a 0.5 mg dose of atropine elevates heart rate, rectal temperature and mean skin temperature; (2) atropine exerts its peak physiological effects approximately 70 minutes after intramuscular injection; (3) within the dosage levels tested, the magnitude of the elevated heart rate response is curvilinearly related to atropine dosage, whereas, the magnitude of the elevated rectal temperature response is linearly related to atropine dosage; (4) repeated administration of atropine over a number of days does not alter thermoregulatory responses; (5) heat acclimation improves exercise-heat performance of individuals under the influence of atropine by enabling a reduced rectal temperature; and (6) heat acclimation increases the sweat output of individuals under the influence of atropine; however, the absolute reduction in sweat output from atropine is the same pre- and post-heat acclimation.

INTRODUCTION

During military operations in hot environments, the combined metabolic and environmental heat stress must be dissipated by the soldier to enable sustained physical exercise performance. Physical exercise can routinely increase metabolic heat release (M) by ten to thirty times the basal rate, requiring resultant thermoregulatory adjustments for heat dissipation. The primary physical mechanisms for heat dissipation from the body to the environment are: radiation, convection and evaporation. The classic energy balance equation for evaluating heat gain (or heat loss) from the body is written as follows:

$$S = M - (\pm W) \pm (R+C) - E$$

where S = rate of body heat storage

M = rate of metabolic energy release

W = the mechanical work of exercise

$R+C$ = rate of radiant and convective energy exchanges

E = rate of evaporative heat loss

However, the relative magnitude that each of these major physical mechanisms contributes to heat dissipation depends upon the specific environmental conditions. For soldiers operating in a desert-type environment, evaporative heat loss by sweating (because of a large skin to ambient air vapor pressure gradient) provides the primary mechanism for thermoregulation. In this environment, R + C would be less able to dissipate heat because of a small or negative skin to environmental temperature gradiant. Therefore, a decreased sweating rate would result in increased body heat storage and reduced physical exercise performance (Wyndham, 1973).

The US Army has currently authorized soldiers to carry three nerve agent antidote injectors, each containing 2 mg of atropine. When exposed to the threat

of organophosphate (anticholinesterase nerve agent) poisoning, soldiers will be directed to self administer the atropine intramusularly. It is also possible that during combat the antidote could be used in the absence of nerve agent challenge. The pharmacological effects of atropine include the prevention of acetylcholine (Ach) from acting on the eccrine sweat gland which results in a suppression of sweating. Atropine exerts this pharacological effect by competing with Ach for binding sites at the cholinergic receptors (Hulme et al., 1978; Yamamura and Snyder, 1974). Therefore, atropine administration by the soldier will result in a reduced sweating rate and ultimately a reduced physical exercise performance (Craig, 1952; Cullumbine and Miles, 1956).

This paper summarizes two studies, conducted at the US Army Research Institute of Environmental Medicine, which investigated the physiological effects of field applicable doses (2-4 mg, i.m.) of atropine on soldiers performing physical exercise in hot-dry environments. Study I determined the threshold for physiological effects and the gradation of these effects with increasing dosage of atropine. Study II examined the effects of exercise-heat acclimation on the reduced physical exercise performance that occurs following atropine administration.

METHODS

Study I

Seven healthy male soldiers served as volunteers for this study. The physical characteristics of the subjects were ($\bar{X} \pm$ SD) age, 24 $\pm$ 3 yrs; height, 174 $\pm$ 12 cm; weight, 76 $\pm$ 3 kg; and body fat, 15 $\pm$ 2%. This study was performed in the early fall when subjects were naturally partially heat acclimatized. The subjects initially completed a four day exercise-heat acclimation program. Following exercise-heat acclimation, eight test days, alternating with rest days

(no drug or heat exposure) were conducted. The first, fourth and seventh test days served as controls, with a placebo dose of normal saline. Test days two, three, five and six were atropine treatment days of 0.5, 1, 2 and 2 mg, respectively. On day eight, various doses of 0.5 to 4 mg were administered.

On test days, subjects dressed in the Temperate Battle Dress Uniform were seated in a comfortable (20°C, 40% rh) antechamber where baseline heart rates (HR), rectal temperatures (T_{re}) and skin temperatures ($\bar{T}_{sk}$) were recorded. Following baseline measurements, placebo or atropine injections were given intramuscularly (vastus lateralis). Within ten minutes, subjects entered the heated chamber (40°C, 20% rh) where two cycles of 10-minute rest and 50-minute exercise (walking 3 mph on a level treadmill) bouts were attempted. Physiological measurements were obtained at rest and during exercise by the procedures previously reported (Shapiro et al., 1980). During each test session subjects were allowed to drink water ad libitum. The test was terminated for any subject whose rectal temperature reached the upper limit of 39.5°C, whose HR exceeded 180 $b \cdot min^{-1}$ for five minutes, or who was removed at the discretion of the medical monitor.

Study II

Eight healthy male soldiers served as volunteers for this study. The physical characteristics of the subjects were age, 23 ± 3 years; height, 181 ± 8 cm; weight, 81 ± 10 kg; and body fat, 15 ± 5%. The study was performed in the early spring when the subjects were not naturally heat acclimatized. Each subject completed a heat stress test on two occasions both before and after completing an exercise-heat acclimation program. One test was conducted following atropine injection and the other following saline injection (control).

Subjects dressed in gym shorts, T-shirts and tennis shoes were seated in a comfortable (20°C, 40% rh) antechamber where baseline physiological measurements were recorded. Following baseline measurements, saline or atropine (2 mg) injections were given intramuscularly (vastus lateralis). Within five minutes, subjects entered the heated chamber (49°C, 20% rh) and attempted an exercise-rest program nearly identical to that described for Study I. However, for this study 10-minutes of rest and 25-minute exercise bouts were employed for a total of 140 minutes. During all test sessions, subjects were allowed to drink water ad libitum. Total body water loss was determined after each 25-minute exercise bout. The remaining procedures and methodology were identical to those described for Study I.

Statistical Analysis: Means, standard deviations, independent and paired t tests, repeated measures analysis of variance, Tukey critical difference tests, and regression analysis were performed on a desktop computer (HP-9825). Statistical significance was accepted at the $P < 0.05$ level.

RESULTS AND DISCUSSION

Study I

No statistical ($p < 0.05$) differences in physiological responses were found between the three placebo dose tests. Therefore, day four was arbitrarily selected as the control day for comparisons among treatments. During the control tests, HR responses remained relatively constant over time, and were significantly ($p < 0.05$) lower than the responses for the three atropine tests. During each of the atropine tests, HR significantly ($p < 0.05$) increased to peak levels by the end of the first exercise bout. Thereafter, HR values did not continue to increase during the second exercise bout. This observation is consistent with data from previous studies (Craig, 1952; Robinson, 1953) and

suggests that atropine's chronotropic effects during exercise reach peak levels after approximately one hour. Generally, HR values were significantly elevated with increasing atropine dose ($p < 0.01$).

During all of the exercise tests, T_{re} values continued to increase throughout the second exercise bout. The T_{re} values were significantly ($p < 0.05$) elevated above control levels with increasing atropine dosage. Craig (1952) have also reported that after atropine administration, T_{re} values continued to increase for sometime after HR values have peaked during exercise-heat stress. The $\bar{T}_{sk}$ values remained relatively constant over time for all of the exercise-heat tests. However, $\bar{T}_{sk}$ values were significantly ($p < 0.05$) warmer with increasing atropine dosage. The warmer $\bar{T}_{sk}$ values for the atropine treated men were probably caused by a decreased sweating and evaporative skin cooling.

Figure 1 presents the change in HR and T_{re} values between the atropine and control trials at 50-minutes of exercise, regressed against atropine dosage for each subject. The HR responses were best described by a quadratic equation, whereas, the T_{re} responses were best described by a linear equation. Craig (1952) has reported that 2 mg of atropine will increase HR values by 37 $b \cdot min^{-1}$ during exercise-heat ($30^{\circ}C$; 80% rh) stress for unacclimated subjects; the present study found a 50 $b \cdot min^{-1}$ increase above control levels for acclimated subjects. Increasing atropine dosage to 4 mg did not cause an additional elevation of HR, suggesting the chronotropic effect to be from vagal inhibition. The increased body temperature during the atropine tests could also have contributed to the elevated HR values. The linear change in T_{re} with atropine suggests that sweating rate was inhibited at a proportional rate with increasing atropine dosage from 0.5 to 4.0 mg. Thus, 2 mg of atropine increased T_{re} responses by $0.7^{\circ}C$ for this experiment.

FIGURE 1 ABOUT HERE

Statistical comparisons between the two 2 mg treatment days were conducted for HR and T_{re} responses for the six subjects who were tested both days. In general, HR responses were about 5% lower on the second 2 mg treatment day compared to the first at 115 $\pm$ 14 and 121 $\pm$ 15 $b \cdot min^{-1}$, respectively ($p < 0.01$). Since HR responses to exercise are easily influenced by many parameters, it is difficult to conclude whether the small reduction in these values are a function of test habituation or reduced parasympathetic inhibition from atropine. The T_{re} responses throughout exercise were not different ($p > 0.05$) between the two atropine treatment days. Final exercise T_{re} values of 38.8°C were found for both the first and second 2 mg atropine tests. The T_{re} responses would not be expected to be influenced by test habituation. Therefore, repeated dosage of atropine does not alter thermoregulatory responses to exercise-heat stress.

Study II

In general, the subjects were able to complete the control test both pre- and post-heat acclimation. The T_{re} responses to exercise were significantly ($p < 0.05$) decreased by 0.6°C during the post- than pre-acclimation control test. Tnese lowered T_{re} responses were accompanied by a significant ($p < 0.05$) increase (113 $g \cdot m^{-2} \cdot h^{-1}$) in total body sweating rate. This increased sweat output after heat acclimation was also probably coincident with a smaller volume of non-evaporated sweat (Gonzalez et al. 1974). Therefore, heat acclimation would enable reduced T_{re} values by increasing the capacity as well as the efficiency of the sweating responses.

During the atropine tests, heat acclimation increased ($p = 0.06$) mean exercise time from 59 ± 14 minutes to 79 ± 42 minutes for the pre-and post-acclimation tests, respectively. The HR values were significantly ($p < 0.05$) reduced by heat acclimation for the control (-21 $b \cdot min^{-1}$) and atropine (-11 $b \cdot min^{-1}$) tests. Atropine was found to increase HR values above control levels by 42 and 52 $b \cdot min^{-1}$ for the pre- and post-acclimation tests, respectively. Although T_{re} responses decreased by 0.2°C during the post-acclimation atropine test, these differences were not significant ($p = 0.14$). Atropine was found to increase T_{re} values above control levels by 0.5 and 1.0°C during the pre-and post-acclimation tests, respectively. The data of Study I estimates that 2 mg of atropine would increase HR by 50 $b \cdot min^{-1}$ and T_{re} by 0.7°C for acclimated subjects. However, direct comparisons between these studies are tenuous because of differences in environmental conditions, subject populations and exercise times.

Figure 2 presents each subject's change in rectal temperature plotted against their change in exercise time for the pre- and post-acclimation atropine tests. A significant ($p < 0.05$) negative correlation coefficient of $r = -0.70$ was found between these variables; suggesting that increased exercise time was related to the lowered T_{re} values. These lowered T_{re} responses were accompanied by a significant ($p < 0.01$) increase (113 $g \cdot m^{-2} \cdot h^{-1}$) in total body sweating rate. Atropine resulted in a significant ($p < 0.01$) reduction in sweat output (-197 $g \cdot m^{-2} \cdot h^{-1}$) from placebo levels during the pre- and post-acclimation tests. This calculates to a 51 and 39% reduction in total body sweating rate for the pre- and post-acclimation atropine tests, respectively. Therefore, heat acclimation enabled improved evaporative cooling by elevating sweat output because it did not influence the absolute amount of sweating inhibition by atropine. Craig (1952) has reported that 2 mg of atropine (i.m.)

resulted in a 48% reduction of sweating rate for unacclimated subjects during exercise-heat stress.

FIGURE 2 ABOUT HERE

Our data indicate that heat acclimation significantly improve the exercise-heat performance of individuals under the influence of atropine; by facilitating the sweat output which increases the evaporative cooling and thereby lowers core temperature responses. Craig et al. (1969) have previously examined the effect of heat acclimation on atropine sweating inhibition for resting subjects in 41 and 52°C environments. Their data indicated that passive heat acclimation did not alter the sweating response when under the influence of atropine (2 mg, i.v.) during resting conditions.

CONCLUSIONS

Based on the results of two recent exercise-heat studies, we make the following new conclusions about atropine.

1. A 0.5 mg dose of atropine results in significant elevations in HR, T_{re} and $\bar{T}_{sk}$ responses during exercise in the heat.
2. Atropine appears to exert its peak physiological effects approximately 70 minutes after an intramuscular injection.
3. During exercise-heat stress the magnitude of the elevated HR response is curvilinearly related to atropine dosage (0.5-4 mg, i.m.); whereas, the magnitude of the elevated T_{re} response is linearly related to atropine dosage.
4. Repeated administration of atropine over a number of days does not alter thermoregulatory responses to exercise-heat stress (with or without atropine administration).

5. Heat acclimation improves the exercise-heat performance of individuals under the influence of atropine. This improved exercise-heat performance primarily results from lowered T_{re} responses.
6. Heat acclimation increases the sweating output of individuals under the influence of atropine. However, the reduction in sweat output from control levels is the same pre- and post-acclimation.

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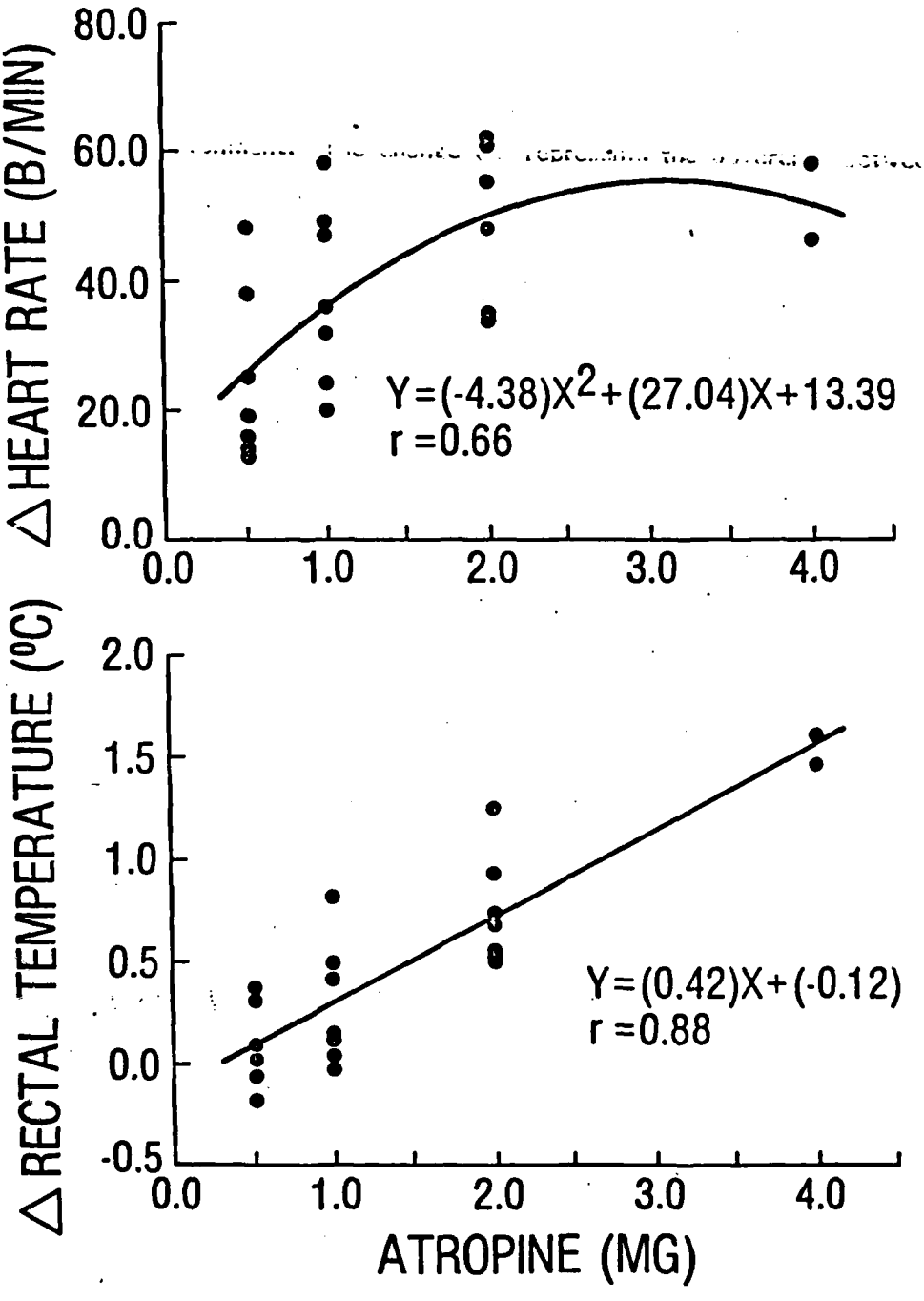
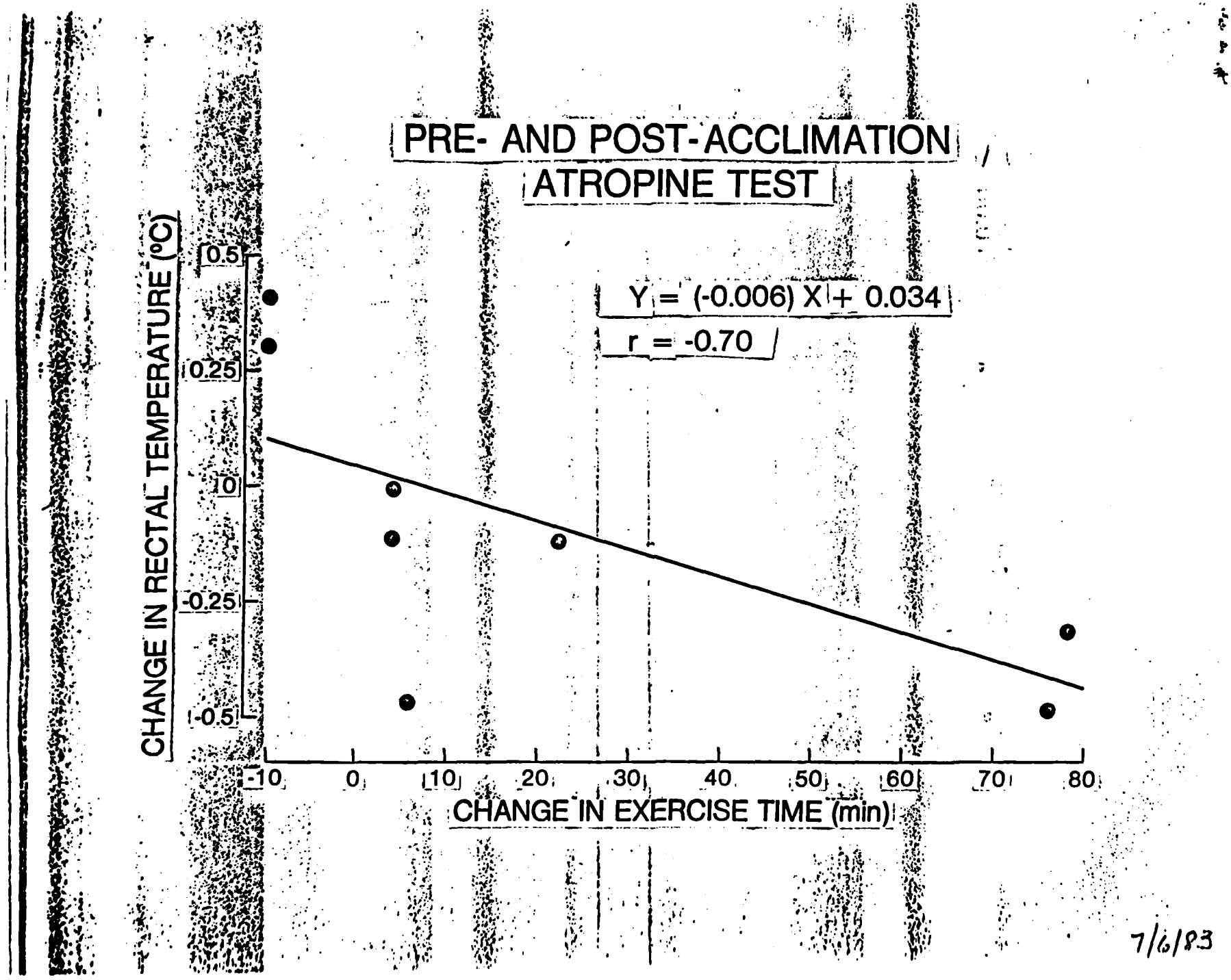
Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

FIGURE LEGENDS

FIG. 1. Effects of atropine dose (i.m.) on the heart rate and rectal temperature responses to light intensity physical exercise in a hot environment. The change (Δ) represents the difference between the responses to the control and atropine exercise tests.

FIG. 2. The relationship between the change in rectal temperature and change in exercise time between the control and atropine exercise test in a hot environment.


80.0
60.0
40.0
20.0
0.0
Δ HEART RATE (B/MIN)
Y=(-4.38)X2+(27.04)X+13.39
r =0.66
0.0
1.0
2.0
3.0
4.0
2.0
1.5
1.0
0.5
0.0
-0.5
Δ RECTAL TEMPERATURE (°C)
Y=(0.42)X+(-0.12)
r =0.88
0.0
1.0
2.0
3.0
4.0
ATROPINE (MG)


PRE- AND POST-ACCLIMATION
ATROPINE TEST
Y = (-0.006) X + 0.034
r = -0.70
CHANGE IN RECTAL TEMPERATURE (°C)
0.5
0.25
0
-0.25
-0.5
-10
0
10
20
30
40
50
60
70
80
CHANGE IN EXERCISE TIME (min)

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